Assembling a Global Vaccine Development Pipeline for Infectious Diseases in the Developing World

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Commercial realities have drastically reduced private investment in the development of new public health tools, but increased awareness of this situation has resulted in the emergence of a variety of research-based, nonprofit organizations. We reviewed current vaccine developments and developed a framework for efficient research and development investments in this area.

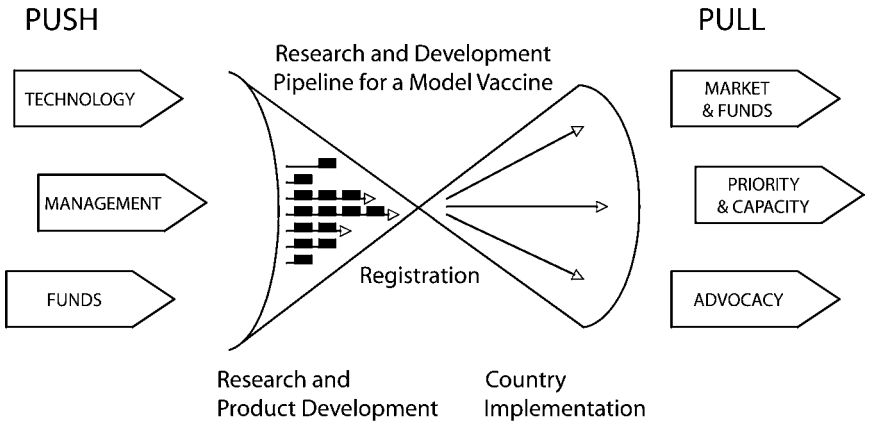
We have identified several key "push" and "pull" forces within the vaccine research and product development environment and have examined their impacts on the process. These forces affect the global vaccine pipeline, which is composed of all individual vaccine initiatives and global partnerships (i.e., stakeholders), All of these research and development stakeholders must work together to establish and promote a global, sustainable research and development pipeline that delivers optimal vaccines and immunization technologies. (*Am J Public Health.* 2006;96:1554–1559. doi:10.2105/AJPH.2005.074583)

VACCINES ARE THE cornerstone of the fight against communicable diseases. This has been proven by the success of smallpox eradication, the drastic reduction in polio cases during the past 20 years, the progress toward tetanus elimination, and the reduction of measles mortality. Despite these achievements, infectious diseases are still responsible for nearly 30% of all deaths worldwide; more than 15 million people die every year, mostly in low-income and middle-income countries.[1] Approximately 1.5 million of these deaths could have been prevented if the currently available vaccines were made universally available. Additionally, licensed vaccines to combat many deadly childhood diseases do not yet exist (Figure 1).[2]

Achievement of the United Nations (UN) Millennium Development Goals relies in part on the availability of new tools through research and product development, innovation, and breakthroughs. Goals (such as halving current child mortality figures by the year 2015 [Goal 4]; combating HIV/AIDS, malaria, and other diseases [Goal 6]; forging a global partnership for development; and partnerships ensuring access to medicines [Goal 8]) are highly pertinent to the vaccine community. In 2005 the World Health Assembly adopted an ambitious and comprehensive plan, the Global Immunization Vision and Strategy 2006-2015 (GIVS), for fighting vaccine-preventable diseases.[3] This strategy has 3 priority objectives: (1) immunize more people against more diseases, (2) introduce a range of newly available vaccines and technologies, and (3) provide a number of critical health interventions through immunization. Development of new and improved vaccines, and enhanced coverage for old and new vaccines alike, will contribute substantially to global efforts to reduce disease burden and, in so doing, will reduce poverty.

DRIVING FORCES FOR RESEARCH AND DEVELOPMENT

The research and product development process bridges the



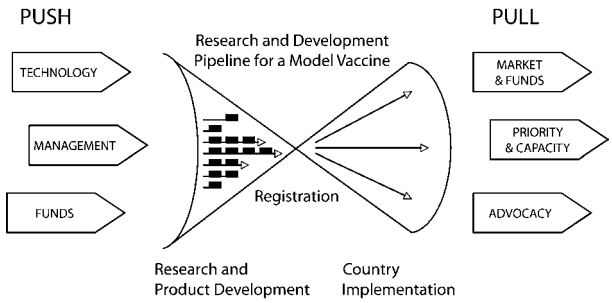
Note. "Neonatal causes" includes infectious diseases (neonatal tetanus, pneumonia, meningitis, sepsis/septicemia, diarrhea and other infections during the neonatal period) as well as noncommunicable diseases (birth asphyxia, congenital abnormalities, and preterm birth). "Others" represents mortality in 10% of children aged younger than 5 years and includes causes unrelated to AIDS, diarrhea, measles, malaria, acute respiratory disease, and neonatal causes and injuries.

FIGURE 1—Causes of death in children aged younger than 5 years.

gap between scientific discovery and the delivery of tools for health intervention. Vaccines used today are the product of discovery and development during past decades. The aim of the research and product development process[4] is to design effective and consistent methods for the identification and production of potential vaccines, test them for safety and efficacy in preclinical studies, and establish their efficacy in humans. There is a clear responsibility throughout vaccine development to both adhere to and be guided by a structured framework that embodies registration requirements and normative guidelines. This framework collectively ensures the ethics, safety, and quality of the research, manufacturing, and clinical development during the research and product development process.

It often takes more than 10 years to deliver a final, licensed vaccine,[5] and requires not only excellence during research and product development but also managerial and funding commitment throughout the endeavor. The cost of developing a vaccine—from research and discovery to product registration—is estimated to be between US $200 million and US $500 million per vaccine.[6] This figure includes vaccines that are abandoned during the development process. In short, vaccine research and product development is lengthy, complex, and loaded with binary outcome risks.

Several driving forces have an impact on the research and product development process that develops vaccines for nonprofit or low-profit markets that can be grouped into 2 categories: "push" and "pull"—terms that are commonly used when business strategies are being developed. Abstractly, a product is developed either because of a clear demand—a "pull"—for the vaccine in the marketplace or because it becomes technically and operationally feasible—a "push." In practice, the actual delivery of the product to the population in need is dependent on the concerted action of both forces (Figure 2).



Note. The shape of the cones mimics a balloon pushed and pulled through the "eye" of the registration "needle." The arrows inside the cones represent the movement along the Push and Pull continuum. Black boxes represent potential vaccine candidates that will eventually yield 1 licensed product.

FIGURE 2—Driving forces for public health research and product development.

Within the context of vaccine development, push forces are principally composed of scientific and technological advances, management and coordination support, and availability of research and product development funding. Pull forces reflect governmental and public recognition and commitment to the fulfillment of health needs and the potential profitability of a future product within a specific free-market segment.

Balancing both forces is necessary for establishing a sustainable product pipeline that consistently yields new vaccines and contributes new public health tools. Additionally, the reality of these forces must be credibly articulated in language that resonates with all stakeholders (i.e., immunization partners). Investing resources and efforts that strengthen any of the push and pull forces can affect the product-oriented pipeline and the impact of unilateral (i.e., asymmetric) disturbances on any point of the process. This investment should be viewed holistically within the context of the entire development environment. In the commercial world, all push forces are united by company operations that target either existing or emerging markets. With publicly funded research, there is additional complexity because of numerous independent entities that have their own discrete mandates.

Technology Push

During the past few decades, scientific advances in fields such as biotechnology, immunology, bioinformatics, genomics, and proteomics and the development of DNA-based and peptide-based vaccine technologies have provided large numbers of potential new molecules that can be selected for vaccine development. Preclinical vaccine-testing platforms and new approaches to the development of animal models of disease (such as transgenic animals, i.e., animals that have been genetically altered to exhibit disease symptoms) have moreover broadened the range of potential approaches for validating the potential vaccine. Finally, innovative drug delivery methods and improved understanding of pharmaceutical formulation and clinical testing allow for the potential enhancement of both existing and potential vaccines. Several publicly funded research funding entities—including the National Institutes of Health (NIH), the Medical Research Council, the US Agency for International Development (USAID), the World Health Organization's (WHO) Initiative for Vaccine Research, the United Nations' Children's Fund (UNICEF)-United Nations' Development Programme (UNDP)-World Bank-WHO Special Programme for Research and Training in Tropical Diseases, the Program for Appropriate Technology in Health, and the International Vaccine Institute—are actively involved in these efforts.

It is appropriate to use technology as the departure point for promoting collaborative initiatives.

Because science is a common language, technology exchanges between established and developing health initiatives, as well as between north and south and south and south countries, can be readily implemented. The ultimate goal of these networks is to focus collective research efforts on the challenges within disease-endemic countries. The effective engagement of all research communities can ensure that the issues most relevant to health are addressed with the most effective technological approaches available.

Research and Product Development Funds Push

Developing countries' public spending on research and product development is insufficient for supporting effective internal development of new or improved tools that combat the wide spectrum of infectious diseases in these countries. The low capacity that is the result of internally derived funds has recently been bolstered by a positive trend in contributions from industrialized countries to the developing world. This funding has come from bilateral development agencies, including USAID, the Canadian International Development Agency, the United Kingdom's Department for International Development, and the Swedish International Development Agency; multilateral organizations, including WHO, the UNDP, the World Bank, and the European Commission, and public and private foundations and grant support programs, including NIH, the Rockefeller Foundation, the Wellcome Trust, and the Bill and Melinda Gates Foundation. However, despite this increase in funding, research and product development funds for vaccine research are still insufficient.

Management Push

Effective vaccine research and product development relies on efficient management and access to long-term committed resources. Without effective and experienced management, successful vaccine development is virtually impossible, because the process is both complex and lengthy. During the past 2 decades, several international initiatives, public–private partnerships, and alliances have been created and are active in vaccine research and product development, including the UNICEF-UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases, the Program for Appropriate Technology in Health, and the International Vaccine Institute. Several entities that are focused on single diseases—including the Aeras Global TB Vaccine Foundation, the International AIDS Vaccine Initiative, and Program for Appropriate Technology in Health's Malaria Vaccine Initiative—have been created to manage product development processes.

In addition to these initiatives, many established programs and dedicated international and national institutions have provided ad hoc support, advocacy, and funds for managing vaccine research and product development projects.[7] Often, these new research and product development initiatives (e.g., the International AIDS Vaccine Initiative) have responsibility for all product-related push forces (technology, funds, and management) that are supported by fundraising and advocacy, although for the most part, their coordination with disease control programs and vaccine procurement mechanisms still needs to be effectively integrated.

Market and Procurement Funds Availability Pull

Today, all publicly funded vaccine research and product development require at least 1 industrial partner, or at a minimum 1 established manufacturing entity, because of capital expenditure barriers resulting from the need to produce vaccines in accordance with good manufacturing practices. For the industrial partner, factors that have an impact on the minimum level of pull forces necessary for attracting significant funding are the same whether the products are developed for the developing world or for an established market economy. These factors include developmental and commercialization costs and risks, which culminate in the risk-adjusted chance of generating acceptable stakeholder return from a finite budget.

Throughout the decisionmaking process about whether to favor one development program over another, opportunity costs prevail, i.e., the value of using resources in one way versus the value of pursuing other available alternatives. The commercial third party considers the minimum acceptable market pull forces in a public–private partnership to be where the opportunity cost is neutral. The public sector realizes it must consider the expected return of a specific investment in terms of public health gain rather than invest limited resources in competing priorities. For example, the Global Alliance for Vaccines and Immunization is currently developing and testing framework-based investment cases for future fund allocation. The combination of developmental risks and manufacturing risks, compounded by politically and economically driven uncertainties in the end-consumer marketplaces, collectively often result in unattractive investment propositions for commercial vaccine development organizations.[8]

To overcome the vacuum left by the lack of an innate market pull, it has been proposed that public funds be set aside to guarantee procurement of new vaccines at a fixed price during a predetermined time period.[9] If uncertainty in the commercialization risk is reduced well in advance, developmental risk becomes the main variable that the managerial decisionmakers must consider. Reducing the risk should facilitate the inclusion of vaccines in a commercial product portfolio. This approach has already been effective. For example, public sector increases in procurement commitments and funding has been successful in attracting commercial entities to invest in the development and production of the relatively

low-cost hepatitis B and combination vaccines for developing markets. In the future, there may be investments in rotavirus and pneumococcal vaccines once they are introduced.

Control Priorities and Health Systems Capacity Pull

Governments are the key players in the formulation and implementation of national immunization policies. Public sector entities, such as international organizations and disease control programs, should therefore provide countries with sufficient information about disease burden and the cost-effectiveness of new vaccines, which will allow governments to include evidence-based decisions about the introduction of new vaccines in their immunization programs. If governments present clearly articulated and consistent national program policy statements about the introduction of new vaccines, including recommendations from international partners, global demand for new products can be better ascertained and used as a pull factor to stimulate vaccine research and product development.

Additionally, major investment is necessary for strengthening health systems before the introduction of new products. Indeed, the health systems in many developing countries are struggling to sustain their existing vaccine programs. Today, many international agencies, alliances, nongovernmental organizations, and bilateral initiatives—including WHO, UNICEF, the World Bank, and the Global Alliance for Vaccines and Immunization—are helping national governments to strengthen their immunization and health systems. Future strengthening of health systems should overcome this capacity barrier and lead to the development of a more dependable pull force for vaccine research and product development efforts.

Advocacy Pull

Evidence-based advocacy can have a great impact on attracting the attention of researchers and funding bodies for vaccine development projects. Surveillance data, global and national burden of disease estimates, and demand projections can emphasize the true health value of particular research and product development investments. Through this process, investment in neglected diseases may potentially be rendered more attractive for commercial development and may have an increased likelihood of attracting public funds and management efforts. Advocacy support is therefore important for the sustainability of research and product development programs and for the delivery of nonmonetary credits to all partners who contribute to the enterprise.

The existence of push and pull forces, and an appropriate balance between them, is necessary for establishing a sustainable product pipeline. The odds for research product attrition rates are dictated by empirically determined probabilities of success. Several potential, independently produced products should be pulled and pushed into the pipeline to beat these odds, which will result in at least 1 licensed product eventually being launched. The driving forces should not favor one potential vaccine or clinical trial. Rather, the forces should favor an entire product pipeline of numerous projects to promote fair competition and diversification of research approaches. The result will be successful, sustainable pipelines of research projects that will deliver tools for future efficient global immunization efforts (Figure 2).

The imbalance of forces, or the lack of 1 or some of them, impairs the formation of an efficient research and development pipeline. The malaria vaccine research and product development is a case in point, because, during the past 3 decades, effective push forces (substantial investment by academic institutions into upstream research, availability of the complete sequence of the *P. falciparum* genome, etc.) were insufficient for establishing a credible product pipeline. The recent creation of 2 initiatives dedicated to malaria vaccine research and development—the European Malaria Vaccine Initiative and the United States' Malaria Vaccine Initiative—has provided an additional element in the form of a management and funding push. The previously modest pull forces also have been reinforced. The Malaria Research and Development Alliance intends to increase the level of advocacy for malaria interventions, and USAID and the Malaria Vaccine Initiative have conducted a study in Africa that assessed the future market for a malaria vaccine. It is hoped that a clearer definition of the demand (market pull) for such products will stimulate industry investment in this area and accelerate discussions within ministries of health about strategies for introducing this prevention tool (health priority pull).

Finally, the malaria vaccine research and product development community has recently completed a technology road mapping exercise, which the industry is using to define new pathways for innovation and increased efficiency. The goal of technology road mapping is to accelerate and improve the development of promising malaria vaccines by providing a cohesive framework for defining critical needs, focusing technology investments, producing a blueprint to align and guide activities within the global malaria community, catalyzing new investment, and directing donor funds to the highest-priority needs. In addition to these promising malaria vaccine efforts, several recent investments in dedicated research and development funding, technologies, and management—in the form of nonprofit enterprises[10–12]—also bring hope for a breakthrough in other vaccine research and development, including HIV and tuberculosis.

All these driving forces are instrumental in ensuring that enough potential vaccines are moved through the research and product development process and that 1 or more effective products will eventually be licensed and introduced into immunization programs. In this manner, the concept of a global vaccine research and product development

portfolio pipeline emerges by combining all the individual efforts and initiatives for researching and developing vaccines that target infectious diseases.

A GLOBAL VACCINE RESEARCH AND DEVELOPMENT PIPELINE ALREADY EXISTS

The various vaccine research and product development stages include discovery, preclinical research, clinical and regulatory research, and postlicensing research. Because of this process, work on future access to vaccines should be undertaken early for all infectious diseases in developing countries. To increase both the efficiency and the probability of successful outcomes for individual vaccine-related initiatives, the work of all partners should be viewed as the component elements of a concerted global effort. The integrity of the individual entities will be respected, and an informally integrated and common global pipeline can emerge (Table 1).

Vaccine research and product development is a high-risk undertaking. From a statistical view, the global product pipeline requires many early-stage development projects to generate 1 successful product; the probability of a preclinical vaccine reaching the market has been estimated at 0.22, i.e., about 5 to 1 odds against success. As a result, to register a single vaccine, there needs to be 4 to 5 independent potential vaccines under development.[5] The uncertainty of research outcomes makes establishing and maintaining such a pipeline a necessity. To ensure the likelihood that a vaccine will actually emerge on the market, the pipeline must be composed of a research and product development portfolio of different potential vaccines in different stages of development for each of the targeted diseases and postregistration activities that will ensure future accelerated introduction and access of vaccines.

Certain gaps can be identified in the current global vaccine pipeline. For example, there is only 1 potential recombinant vaccine for leishmaniasis (supported by the Infectious Disease

TABLE 1—Global Vaccine Research Development Pipeline

Disease or *Pathogen*	Major Partners Promoting Vaccine Development Against Diseases of Developing World	Most Advanced Candidate Stage			Research for Introduction
		Discovery	Clinical	Postregistration	
HIV	ANRS, IAVI, MRC, NIH, private sector		X		X
Malaria	EMVI, EU, MVI, NIH, USAID, private sector		X		X
Tuberculosis	Aeras, EU, NIH, private sector		X		X
Influenza (broad spectrum)	EU, NIH, private sector	X			
Pneumococcus	EU, Johns Hopkins pneumoADIP, MRC, NIH, PATH, USAID, private sector			X	X
Cholera	IVI, NIH, private sector			X	X
Enterotoxigenic *Escherichia coli*	CVD, private sector		X		
Rotavirus	CDC, PATH rotaADIP, USAID			X	X
Shigellosis	CVD, IVI, NIH, WRAIR, private sector		X		
Typhoid	IVI, NIH, private sector			X	
Caliciviruses	CDC, CVD		X		
Dengue	PDVI, WRAIR, private sector		X		X
Japanese encephalitis	PATH, private sector			X	X
Hookworm	Public sector		X		
Leishmaniasis	IDRI, public sector		X		
Schistosomiasis	EU, NIH, USAID		X		
Buruli ulcer	GBUI		X		
Neisseria meningitides A,C,W135,Y	MVP, private sector			X	X
Streptococcus A	NHMRC, NIH, private sector		X		
Streptococcus B	NIH, private sector		X		
Trachoma	Private sector		X		
Herpes simplex virus 2	NIH, private sector		X		
Human papilloma virus	IARC, NIH, PATH, private sector			X	X
Measles (aerosol)	ARC,CDC, WHO, private sector		X		

Note. ADIP = accelerated development and introduction plan; Aeras = Aeras Global Tuberculosis Vaccine Foundation; ANRS = Agence Nationale de Recherches sur le Sida (France); ARC = Amercian Red Cross; CDC = Centers for Disease Control and Prevention (USA); CVD = Center for Vaccine Development (USA); EMVI = European Malaria Vaccine Initiative; ETEC = Enterotoxigenic *Escherichia coli*; EU = European Union (funded projects), Hib = *Haemophilus influenzae* type b; HIV = human immunodeficiency virus; HPV = human papillomavirus; HSV = herpes simplex virus; GBUI = Global Buruli Ulcer Initiative; IAVI = International AIDS Vaccine Initiative; IDRI = Infectious Disease Research Institute; IVI = International Vaccine Institute; MRC = Medical Research Council (England); MVI = Malaria Vaccine Initiative at PATH; MVP = Meningitis Vaccine Project; NHMRC = National Health and Medical Research Council; NIH = National Institutes of Health (USA); PATH = Program for Appropriate Technology in Health; PDVI = Paediatric Dengue Vaccine Initiative; USAID = United States Agency for International Development; WHO = World Health Organization; WRAIR = Walter Reed Army Institute of Research. Although this review focuses on international and national entities supporting global vaccine research initiatives, it is of note that the private sector and developing country institutions also greatly contribute to the global pipeline.

Research Institute) that has entered clinical trials in the United States and Latin America. In the case of malaria, many potential vaccines concentrate on the same parasite proteins, which potentially repeats similar trial results while neglecting novel target opportunities. For bacterial pneumonia, the current vaccines do not cover all of the disease serotypes required in developing countries, and new vaccines would need substantial investment to reach the market. For human papillomavirus and cervical cancer, the issue of vaccine accessibility among adolescent girls in poor countries has not been adequately addressed, and vaccines have been licensed in 2006 without sufficient data for an effective introduction in developing countries.

The importance of carrying out research in a true partnership with developing countries should not be underemphasized. To ensure the global pipeline operates efficiently and delivers optimal vaccines to poor countries, all of the partners must coordinate their efforts to strengthen research, product development, regulatory evaluation, ethical evaluation, and postmarketing surveillance. Moreover, the participation of developing countries in setting research priorities and defining the most appropriate target product characteristics for new vaccines is essential for the future success of vaccine development and implementation.

Even when efficient vaccines are developed and introduced, research and product development cannot then cease. Implementation research, postmarketing surveillance, and additional clinical studies that enable optimal evaluation in the target population and of the impact of immunization are all necessary and vital components of successful vaccine introduction and deployment. Collectively, these postapproval activities ensure the maximization of a vaccine's life-saving impact. Similar to the life-cycle management approaches that are applied to commercial vaccines, innovation and research that is focused on providing both better vaccines and enhanced vaccine delivery systems and improving the manufacturing process to continually reduce vaccine unit cost to the end-user also should continue. In short, the existence of an "ever-green" (always updated) vaccine pipeline that constantly delivers new or improved products to the market is critical.

CONCLUSIONS

Despite positive trends, the current level of investment in building sustainable research and product development driving forces has not yet reached a sufficient level. The apparently complex global pipeline does not cover all essential aspects of the vaccine development continuum. There are many gaps in this continuum that prevent successful delivery of some essential vaccines. Additionally, the participation of developing countries' research and disease-control entities during the process is often underweighted.

To meet the challenges of the United Nations' Millennium Development Goals, a new coordinated vaccine research and product development paradigm needs to be built through the active participation of all stakeholders. In addition to this convergence of efforts and increased coordination, developing countries should play a central role in identifying and communicating the specific vaccine products they need. WHO will be a critical player in ensuring that all occur. ■

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Note. *The views expressed in this article are those of the authors and do not necessarily represent the policy of the World Health Organization.*

Contributors

Both authors originated ideas, interpreted findings, and wrote the article.

Human Participant Protection

No protocol approval was needed for this study.

References

1. World Health Report 2004, World Health Organization, Geneva, Switzerland. Available at: http://www.who.int/whr/2004/en/. Accessed July 1, 2005.

2. World Health Report 2005, Annex Table 3, World Health Organization, Geneva, Switzerland. Available at: http://www.who.int/whr/2005/en/. Accessed July 1, 2005.

3. Global Immunization Vision and Strategy 2005, World Health Organization, Geneva, Switzerland. Available at: http://www.who.int/gb/ebwha/pdf_files/WHA58/A58_12-en.pdf and http://www.who.int/gb/ebwha/pdf_files/WHA58/A58_12Add1-en.pdf. Accessed July 1, 2005.

4. Initiative on Public-Private Partnerships for Health (IPPPH). Available at: http://www.ippph.org/. Accessed July 1, 2005.

5. Struck MM. Vaccine research and product development success rates and development times. *Nat Biotechnol.* 1996;14:591–593.

6. Andre FE. How the research-based industry approaches vaccine development and establishes priorities. *Dev Biol (Basel).* 2002;110:25–29.

7. Davey S, ed. *The 10/90 Report on Health Research 2001–2002.* Arusha, Tanzania: Global Forum for Health Research; 2002.

8. *Lessons Learned: New Procurement Strategies for Vaccines. Final Report to the GAVI Board.* Mercer Management Consulting; 2002. Available at: http://www.vaccinealliance.org/resources/lessons_learned_draft_final.pdf. Accessed July 1, 2005.

9. Levine R, Kremer M, Albright A. Making markets for vaccines. Ideas to action. Available at: http://www.cgdev.org/doc/books/vaccine/MakingMarkets-complete.pdf. Accessed August 4, 2006.

10 International AIDS Vaccine Initiative. Available at: http://www.iavi.org/. Accessed July 1, 2005.

11. Klausner RD, Fauci AS, Corey L, et al. The need for a global HIV vaccine enterprise. *Science.* 2003;300:2036–2039.

12. Aeras Global TB Vaccine Foundation. Available at: http://www.aeras.org/. Accessed July 1, 2005.